

FROM MINISATELLITES AND GENES: WHEN DO GERMINAL MUTATIONS OCCUR. H Mohrenweiser. Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, Livermore CA 94550

Utilization of molecular techniques has provided insight into the molecular character and origins of spontaneous and induced germinal mutations. Review of the variants at disease loci suggests differences among loci in the frequency of nucleotide substitutions and more complex events. Mechanistic features associated with the alterations in DNA structure are observed in each variant class. The spectrum of mutations identified reflects the gene structure and the selective pressure generating disease phenotypes, and the techniques employed to screen for variation. Locus specificity in spectra has the potential to compromise estimates of increases in germinal gene mutation rates.

Recent studies have identified mosaicism, rather than *de novo* mutation, as the explanation for the non-traditional pattern of inheritance of disease in some families. Mosaicism is a concern for studies of induced mutation rates as it reflects embryonic exposure of the parent of the proband. This is in contrast to the "normal expectation" that induced mutations result from parental exposure to genotoxins in the environment. Observations suggest that the germ cell stage sensitivity may reflect interaction of the mutagen and the loci screened. The mosaicism and germ cell stage issues, in conjunction with incomplete ascertainment of mutational events, increase the complexity of efforts to estimate induced germinal mutation rates and associated health consequences in populations exposed to genotoxic agents.

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